Original Article

Chemotherapeutic Drug-Induced Nail Changes: A Prospective Observational Study

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Abstract

Background: Nail changes associated with chemotherapeutic drugs are common and can compromise the quality of life of cancer patients if left overlooked by a clinician. **Aim:** The aim of this study was to study the common pattern of nail changes caused by chemotherapeutic drugs. **Materials and Methods:** A single-institutional prospective observational study was conducted for patients with histopathologically proven malignancy without prior nail changes undergoing first-line systemic chemotherapy. Analysis of frequency distribution and associations of categorical variables was performed by Chi-square test and multivariate analysis, using IBM SPSS statistics version 21 for Windows. $P \leq 0.05$ was considered statistically significant. **Results:** The incidence of nail changes in the present study was 42% (182 out of 434 cases). Nail changes were commonly observed following 1–2 cycles of chemotherapy, and most of them were Grade 1 changes. The most common nail change observed was chromonychia (49%), followed by onychorrhexis (29%). Chemotherapeutic drugs frequently associated were taxane (65.3%) and platinum compounds (57.7%). Nail changes found associated with taxane included the largest varieties, i.e., chromonychia, onychorrhexis, splinter hemorrhage, Terry's nail, half-and-half nail, Beau's lines, onychodystrophy, and paronychia. Nail changes associated with platinum drugs were onychorrhexis and chromonychia. Adriamycin, bleomycin, vinblastine, and dacarbazine regimen was associated with leukonychia. Adriamycin and cyclophosphamide both were independently associated with chromonychia. **Conclusion:** A knowledge of chemotherapy-induced nail changes can avoid inadvertent diagnostic interventions and improve the quality of life by timely and proper patient counseling.

Keywords: Cancer, chemotherapy, drug, nail changes

Introduction

Cancer chemotherapeutic drugs are associated with different nail changes, which might result from one or more of the following proposed mechanisms: (i) damage to the nail matrix, causing aberrant nail plate growth; (ii) nail bed damage; (iii) damage to the proximal nail fold; and (iv) aberrant blood flow to the nail bed.[1,2] The chemotherapy-induced nail changes frequently mimic nail changes associated with many systemic diseases such as rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid antibody syndrome, psoriasis, pulmonary embolism, coronary thrombosis, cirrhosis, congestive cardiac failure, renal failure, nephrotic or nephritic syndrome, anemia, diabetes, porphyria, peripheral vascular disease, liver diseases, malnutrition, Addison's disease, hyperparathyroidism, and acquired immune deficiency infections.[3-8] Development of nail changes among these patients with terminal illness creates anxiety and apprehension and compromises the quality of life.[4] In view of limited prospective data available, we conducted a prospective observational study to find the association of frequent nail changes associated with chemotherapeutic drugs.

Materials and Methods

A prospective observational study was conducted in a tertiary cancer center in East India. The duration of the study was from August 2019 to March 2020. The study was conducted

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as per the Declaration of Helsinki developed by the World Medical Association in 1964. Informed written consent from individual patients and institutional ethical committee approval were obtained prior to patient enrollment in the study. The inclusion criteria of study participants included patients with histopathologically proven malignancy undergoing first-line systemic chemotherapy. Exclusion criteria were dermatological diseases likely to involve nails or primary nail disorders, history of any occupational contact with any chemicals, and pulmonary, cardiac, renal, hepatic, endocrine disorders, which probably could cause the nail changes. Patients with history of drugs like retinoid in the last 6 months that could cause nail changes were also excluded. Co-administration of different drugs along with chemotherapy agents was noted. Nail changes were independently diagnosed clinically by two dermatologists to avoid bias. Baseline nail changes of the patients were noted and photographs were obtained. Patients were followed up during each chemotherapy cycle (every 3–4-week interval according to the chemotherapy protocols). Any new changes of the nail units were recorded and were documented during each follow-up. Grading of nail changes was done using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5 by a dermatologist. Nail discoloration, nail ridging, and asymptomatic nail loss were considered as Grade 1 changes, whereas symptomatic and painful nail loss was considered Grade 2 changes.[9] The statistical analysis was performed by using IBM SPSS Statistics for Windows, version 21.0 (Armonk, NY, USA: IBM Corp). Chi-square test was used to evaluate the association of different nail changes with chemotherapy regimens. Multivariate analysis (MVA) using multivariate analysis of variance technique (with 95% confidence interval) was used to evaluate the association between nail changes and chemotherapeutic drugs, where a nail finding was observed with two or more chemotherapeutic drug-based regimens. "*R*" ≤ "0.05 was considered statistically significant.

Results

In the present study, the total number of cases enrolled after considering its inclusion and exclusion criteria was 434, out of which 182 (42%) developed nail changes during the chemotherapy treatment. The mean age of patients was 50.7 ± 10.5 years (ranges from 29 to 79 years). Male and female patients constituted 40.4% and 59.6%, respectively. Primary sites of malignancies were breast cancer (43.2%), head-and-neck cancer (18.6%), lung cancer (15.3%), cervical cancer (11.5%), ovarian cancer (9.3%), lymphoma (1.6%), and gastrointestinal cancer (0.5%). Different chemotherapeutic regimens found associated with nail changes in the study are illustrated in Table 1. The frequencies of different nail changes associated with chemotherapeutic drugs observed are depicted in Figure 1. The most common type of nail changes was chromonychia, followed by onychorrhexis. The nail changes were commonly observed after completion of 1–2 cycles of chemotherapy (77.6%), followed by completion of ≥3 cycles

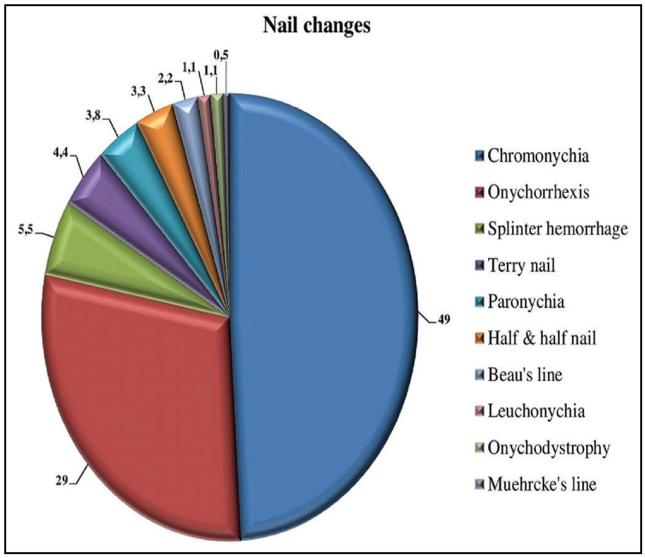

Figure 1: Frequency of different nail changes observed in the study

of chemotherapy (22.4%). Most of the chemotherapy-induced nail changes in the study were Grade 1, i.e., 97% (176) cases had Grade 1 and 3% (6 cases) had Grade 2 nail changes. Few of the common nail changes observed in the study are depicted in Figures 2-4. The association of different nail changes with chemotherapeutic drug-based regimens evaluated by MVA is depicted in Table 2.

Chromonychia was found in those patients who had received paclitaxel, paclitaxel + carboplatin, Adriamycin + cyclophosphamide, docetaxel + carboplatin, docetaxel, cisplatin, 5-fluorouracil + Adriamycin + cyclophosphamide, Adriamycin + cyclophosphamide + paclitaxel, cyclophosphamide + cisplatin, cyclophosphamide, and Adriamycin + bleomycin + vinblastine + dacarbazine regimen. MVA revealed that the drugs associated with chromonychia were paclitaxel, docetaxel, cyclophosphamide, and Adriamycin.

Onychorrhexis was observed in patients who had received cisplatin, paclitaxel + carboplatin, paclitaxel, and carboplatin. MVA revealed that the drugs associated with onychorrhexis were cisplatin and paclitaxel.

Splinter hemorrhage was observed in patients who had received paclitaxel, paclitaxel + carboplatin, and cisplatin. None of the single-agent carboplatin users developed this nail changes. Paclitaxel was associated with splinter hemorrhage in the study, which was not significant in MVA (probably due to lesser incidence of this nail finding).

Terry's nails were found in patients who had received paclitaxel and docetaxel.

Half-and-half nail was seen in patients who had received paclitaxel + carboplatin and paclitaxel whereas not observed among any patients who received single-agent carboplatin.

Table 1: Nail changed associated with different chemotherapeutic regimens

Nail changes	T, *n* (%)	D, *n* (%)	Ci, *n* (%)	Ca, *n* (%)	Cx, *n* (%)	AC, *n* (%)	TC, *n* (%)	DC, *n* (%)	FAC, *n* (%)	TAC, *n* (%)	CC, *n* (%)	ABVD, *n* (%)	*P*
Chromonychia	26 (29.2)	6 (6.7)	6 (6.7)	-	3 (3.4)	13 (14.7)	20 (22.5)	7 (7.9)	3 (3.4)	2 (2.2)	2 (2.2)	1 (1.1)	0.000
Splinter hemorrhage	5 (50)	-	1 (10)	-	-	-	4 (40)	-	-	-	-	-	
Onychorrhexis	6 (11.3)	-	34 (64.2)	4 (7.5)	-	-	9 (17)	-	-	-	-	-	
Terry's nail	5 (62.5)	3 (37.5)	-	-	-	-	-	-	-	-	-	-	
Half-and-half nail	3 (50)	-	-	-	-	-	3 (50)	-	-	-	-	-	
Onychodystrophy	2 (100)	-	-	-	-	-	-	-	-	-	-	-	
Beau's line	-	2 (50)	-	-	-	-	2 (50)		-	-	-	-	
Leukonychia	-	-	-	-	-	-	-	-	-	-	-	2 (100)	
Paronychia	2 (28.6)	2 (28.6)	-	-	-	-	3 (42.8)	-	-	-	-	-	
Muehrcke's line	-	1 (100)	-	-	-	-	-	-	-	-	-	-	

T: Paclitaxel, D: Docetaxel, Ci: Cisplatin, Ca: Carboplatin, Cx: Cyclophosphamide, AC: Adriamycin + cyclophosphamide, TC: Paclitaxel + cyclophosphamide, DC: Docetaxel + cyclophosphamide, FAC: 5-fluorouracil + Adriamycin + cyclophosphamide, TAC: Docetaxel + Adriamycin + cyclophosphamide, CC: Cyclophosphamide + cisplatin, ABVD: Adriamycin + bleomycin + vinblastine + dacarbazine

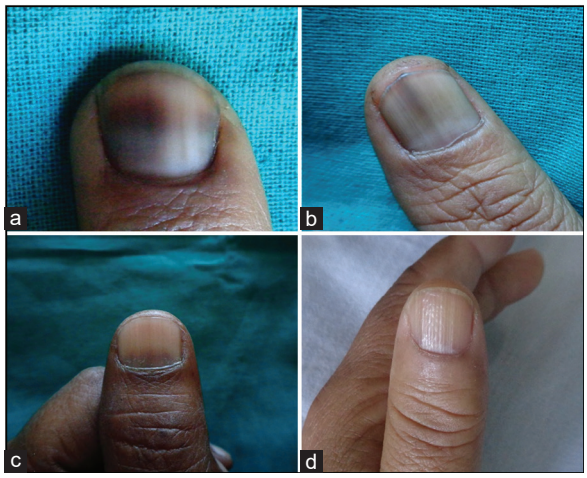

Figure 2: (a-c) Different patterns of chromonychia, (d) Onychorrhexis observed in a patient after receiving two cycles of cisplatin

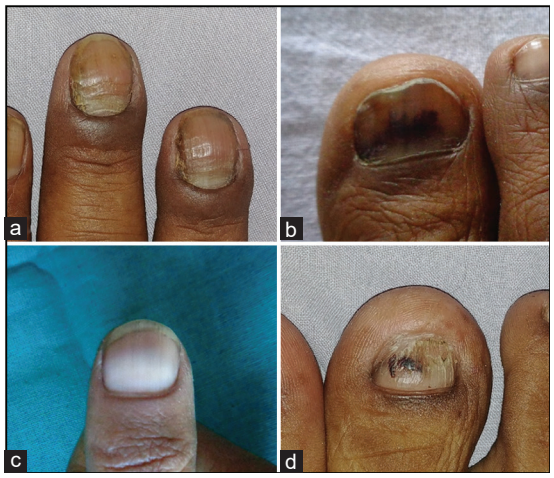

Figure 3: (a) Paronychia in a patient following three cycles of paclitaxel, (b) Splinter's hemorrhage observed in a patient following three cycles of paclitaxel, (c) Half-and-half nail observed in a patient following two cycles of paclitaxel, (d) Onychodystrophy observed in a patient following four cycles of paclitaxel

Beau's lines were observed in patients who had received docetaxel and paclitaxel + carboplatin, whereas it was not observed in any case who had received carboplatin. Onychomadesis was found in two patients after receiving paclitaxel.

Paronychia was observed in patients who had received paclitaxel + carboplatin, paclitaxel, and docetaxel but was not seen among any cases who received single-agent carboplatin.

- Onychodystrophy was observed in patients who had received paclitaxel
- Leukonychia was observed in patients who had received Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) regimen
- Muehrcke's line was observed in one patient who had received docetaxel.

Discussion

The present study was conducted to identify some of the common nail changes and their causative chemotherapeutic agents.

Chromonychia results from activation of melanocytes of the nail matrix and increased production of melanin, although the exact underlying mechanism is not clear. It has been reported to be associated with chemotherapeutic drugs such as Adriamycin, cyclophosphamide, and hydroxyurea.[1,10-13] The drug-induced nail pigmentation proceeds from proximal to distal nail edge, which reverses in a similar fashion after withdrawal of the drugs.[14] The present study found that, in addition to the previous reports of cyclophosphamide and Adriamycin, the other drugs associated significantly with chromonychia were taxane (docetaxel and paclitaxel) and cisplatin. Chromonychia was the most common type of nail change observed in the present study, as similarly reported in the previous study.[15]

Onychorrhexis is multiple longitudinal lines or striations seen on nail plate.[1,16] Its association with specific chemotherapeutic drug is not yet reported to the best of our knowledge. In the present study, it was found to be significantly associated with cisplatin and paclitaxel.

Table 2: Multivariate analysis (95% confidence interval) showing chemotherapeutic drugs associated with specific nail changes

Nail changes	Chemotherapeutic drug-based regimen	*n* (%)	MVA (*P*)
Chromonychia	T	53 (56.4)	0.023
	D	18 (72)	0.013
	Ci	8 (18.6)	0.256
	Ca	34 (54.8)	0.334
	Cx	12 (100)	0.001
	Adriamycin	19 (90.5)	0.000
	ABVD	1 (33.3)	0.589
Splinter hemorrhage	T	8 (8.5)	0.216
	D	-	-
	Ci	1 (2.3)	0.299
	Ca	4 (6.5)	0.665
	Cx	-	-
	Adriamycin	-	-
	ABVD	-	-
Onychorrhexis	T	15 (16)	0.001
	D	-	-
	Ci	34 (79.1)	0.000
	Ca	15 (24.2)	0.354
	Cx	-	-
	Adriamycin	-	-
	ABVD	-	-
Paronychia	T	5 (5.3)	0.273
	D	2 (8)	0.247
	Ci	-	-
	Ca	-	-
	Cx	-	-
	Adriamycin	-	-
	ABVD	-	-
Terry's nail	T	5 (5.4)	0.470
	D	3 (12)	0.047
	Ci	-	-
	Ca	-	-
	Cx	-	-
	Adriamycin	-	-
	ABVD	-	-

MVA: Multivariate analysis, ABVD: Adriamycin + bleomycin + vinblastine + dacarbazine, T: Paclitaxel, D: Docetaxel, Ci: Cisplatin, Ca: Carboplatin, Cx: Cyclophosphamide

Splinter hemorrhage results from micro-injury to the nail bed capillaries.It presents as red, brown, black discolouration of nail, due to extravasation of blood from longitudinally oriented vessels of the nail bed. It is frequently reported after use of vascular endothelial growth factor receptor inhibitors (sunitinib and pazopanib).[1,10,17] In the study, this was found to be associated with paclitaxel, which was in concordance with the previous study report.[15]

Terry's nails are a type of apparent leukonychia, where narrow band of distal nail bed appears normal pink, leaving remaining proximal area of the nail opacified, obscuring the lunula. It is found in cirrhosis of liver, congestive cardiac failure, renal transplant cases, peripheral vascular disease, and type 2 diabetes mellitus.[1,10,18] In the present study, it was found to be associated with taxane (paclitaxel and docetaxel).

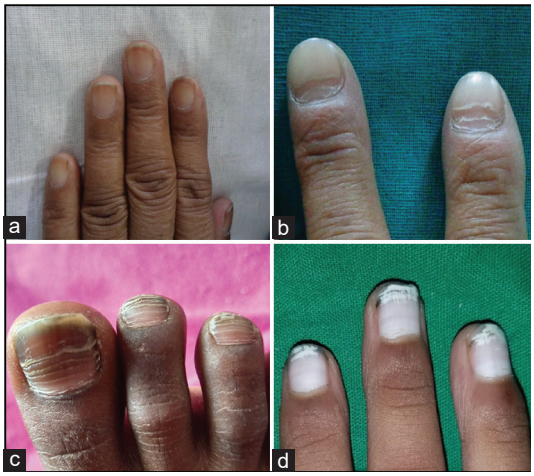

Figure 4: (a) Terry's nail observed in a patient following two cycles of docetaxel, (b) Onychomadesis observed in a patient following the first cycle of docetaxel, (c) Beau's lines observed in a patient following four cycles of docetaxel, (d) Leukonychia observed in a patient following three cycles of Adriamycin, bleomycin, vinblastine, and dacarbazine chemotherapy

Half-and-half nails are a type of apparent leukonychia, where the abnormal white color of the proximal nail fold obscures the lunula. It is found commonly in chronic renal failure patients. It is a reversible nail change, which does not need any specific treatment and disappears after treatment discontinuation.[1,19] In the present study, it was found to be associated with paclitaxel.

Onychodystrophy results from damage to the nail matrix, and it can be congenital, caused by fungal or nonfungal infections, psoriasis, eczema, lichen planus, benign skin warts, or malignancies of skin.[20,21] In the present study, onychodystrophy was observed in two cases, and both cases developed dystrophy after four cycles of paclitaxel.

Leukonychia is white discoloration of nail plate, caused by impaired keratinization of distal nail matrix.This part of nail looks white as light is reflected from the parakeratotic layers of the nail.[1,2] In the present study, leukonychia was observed in two cases after completion of four cycles of chemotherapy with ABVD regimen.

Paronychia results from damage to the perionychium. It can be caused by bacterial or fungal infections secondary to trauma or moisture.[22] It has been reported to be associated with the use of anticancer-targeted therapies such as epidermal growth factor receptor and Erb-B inhibitors (afatinib and lapatinib, respectively) and less likely associated with chemotherapeutic agents (taxane).[10] In the present study, paronychia was found to be associated with taxane chemotherapy (paclitaxel and docetaxel).

Beau's lines are transverse linear depressions on the dorsum of nail plate, caused by temporary cessation of nail growth in the matrix. Multiple Beaus' lines in the same nail denote

multiple exposures to the drug, and the gap between the lines is proportional to the interval between the drug exposures. Beau's lines are reported to be associated with a taxane- and platinum-containing regimen.[1,10,15,23,24] Onychomadesis is an extreme degree of presentation of Beau's lines. In the present study, it was found associated with taxane chemotherapy (docetaxel and paclitaxel).

Muehrcke's line occurs due to abnormality in nail vascular bed and presents as double white transverse lines. It is commonly caused by hypoalbuminemia associated with liver disease, nephrotic syndrome, malnutrition, and chemotherapeutic drugs.[2] In the present study, it was observed in one patient who received docetaxel.

Conclusion

Chemotherapeutic drug-induced nail changes are quite common, which increases anxiety and apprehension among cancer patients. The present study adds information to the available literature on specific nail changes associated with particular chemotherapeutic drug or regimen, which can help a clinician to avoid unnecessary and at times invasive investigations to rule out probable systemic associations. Early diagnosis with appropriate patient counseling can improve the quality of life in these groups of patients with terminal disease.

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Conflicts of interest

There are no conflicts of interest.

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